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Drug–surfactant–propellant interactions in HFA-formulations

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Abstract

The required replacement of chlorofluorocarbon (CFC) with hydrofluoroalkane (HFA) propellants has challenged formulators of pressurized metered dose inhalers in several major respects. Conventional (CFC soluble) surfactants are effectively insoluble in the major CFC replacement candidates, HFA 134 and HFA 227ea, in the absence of co-solvents. While these ethane and propane derivatives have comparable boiling points and vapor pressures to dichlorodifluoromethane (CFC 12), their increased polarity demands that formulators use either alternative (soluble) surfactants, or co-solvents along with traditional surfactants, in order to stabilize pressurized suspension products. The use of either approach is complicated by the existence of many competing patents and the fact that the science in the area is empirical; predictive theoretical approaches are frustrated by the lack of an adequate database. Technical developments in this area must also take into account the need to avoid crystal growth and/or adhesion of micronized, suspended drugs to internal container surfaces, problems which may be catalyzed by some combinations of surfactant type/concentration, vehicle(s) and physical form/type(s) of drug substance. For some drugs, it appears simpler to use co-solvents with HFA propellants to dissolve the drug, avoiding the need for suspension stabilization. This article presents an overview of the present state of the art with respect to the formulation of MDIs.

Keywords: Metered dose inhalers; Aerosols; Propellants; HFA; Formulation; Inhalation

1. Introduction and description of the dosage form

Fig. 1 shows a schematic of the pressurized metered dose inhaler (MDI). Presently, this dosage form may contain chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellants alongside the drug substance, surfactants and co-solvents. Clearly, impurities and drug substance degradation (additional formulation contents outside of the label claim) will depend upon the formulation and the method of manufacture both of ingredients and the final dosage form. The 'replacement' of CFC 11, 12 and 114 with HFA 134a and/or 227ea (Fig. 2) as the propellants in

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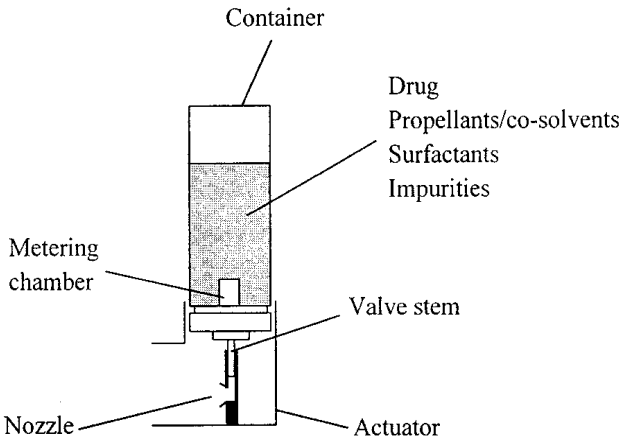

Fig. 1. Schematic of a pressurized metered dose inhaler.

pressurized inhalers, as required by the Montreal Protocol (1989), cannot be accomplished without major additional changes to the dosage form. While the external appearance of the metered dose inhaler may be unchanged, further changes may include modifications to the drug substance, surfactant and co-solvent, as well as valve replacement and actuator redesign. As a result, the process requires substantial experimental review. This article describes the current state-of-the-art with respect to the formulation and reformulation of HFA suspension and solution MDIs, and attempts to fit our current experimental knowledge into a loose theoretical framework. The manufacturing challenges associated with some of the new formulation–packaging combinations (Tansey, 1997) are beyond the scope of this review.

2. General theory of CFC and HFA propelled metered dose inhalers

The paucity of useful theory surrounding the subject of pressurized MDI formulation is due largely to the difficulty of studying formulations containing volatile propellant blends. Consider, for example, the ease with which surface tensions and micellization phenomena can be studied in aqueous systems under ambient conditions. Then transpose this situation to one in which the liquid–gas and liquid–solid interfaces only exist when the propellants are held in equilibrium with their vapors in closed containers. The literature has been complicated by industry's need to replace functional CFC-propelled formulations with those containing hydrofluoroalkanes (HFAs); this has resulted in a wealth of competing patents which make the subject appear to be difficult (Whitman and Eagle, 1994; Byron and Blondino,

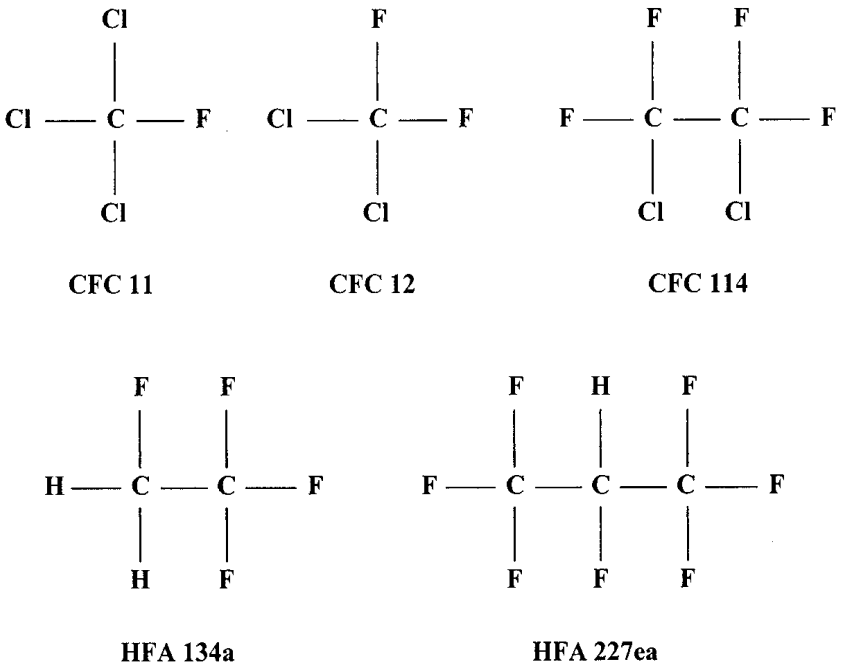

Fig. 2. Chemical structures of CFC and HFA propellants.

1996a,b). Furthermore, the regulatory situations in both Europe and North America now demand that new formulations deliver drug aerosols which are more reproducible (in terms of delivered dose and particle size distribution) than those emitted by the older dosage forms. Thus, some ten years following the signing of the Montreal Protocol, it is appropriate to attempt to answer the question 'where are we now with respect to our knowledge of drug–surfactant–propellant interactions in HFA formulations?'

We should begin our answer with a fundamental observation that has little to do with formulation science: while most of this article will describe important characteristics of materials held, under pressure, inside a container, the industry, and the end user, care only about the characteristics of what comes out of the inhaler mouthpiece. For this reason, efforts to produce, for example, drug suspensions in propellants which exhibit 'controlled flocculation', may or may not be important with respect to the formation of the aerosol spray; this because correlations between the characteristics of the liquid formulations inside the canister and the aerosol spray which leaves the mouthpiece should not be assumed to exist. For example, both flocculated and deflocculated pressurized suspensions may spray successfully from the nozzle of a metered dose inhaler, thus illustrating the importance of using 'delivered dose' and 'aerodynamic particle size distributions' (the primary characteristics of the aerosol sprayed from the mouthpiece) as the major variables to be controlled and measured, when performing formulation research on these systems. The discussion below is not an exhaustive survey of the literature; rather an attempt has been made to abstract some of the more important points and describe these from the point of view of the MDI product formulator.

2.1. Effects of major formulation variables

All workers in the field should read the landmark publications upon which our knowledge is founded. Even though the original Riker patent (Riker Laboratories, Inc., 1960) on CFC-based suspension and solution MDIs and the classic work published by Polli et al. (1969) are old and based upon work in CFC propellants, they, and others quoted below, remain valid for HFA-formulations. Polli et al. (1969) made a series of comparisons between different suspension formulations of dexamethasone. They established some of the effects of suspension and surfactant concentrations, propellant vapor pressure, and spray orifice diameter upon output particle sizes. The latter were determined using cascade impaction following effectively complete propellant evaporation. In effect they observed that high vapor pressure suspensions, with low non-volatile ingredient (drug and surfactant) concentrations produced smaller (more respirable) aerosols. This work formed part of the basis for that of Moren (Moren, 1978a,b, 1980; Newman et al., 1981, 1982) in which he developed spacer and reservoir chambers to enable further propellant evaporation and shrinkage of aerosol droplets prior to patient inhalation. Moren's work noted the crucial importance of minimizing the metered volume, for a given concentration of non-volatile ingredients, in order to produce smaller, more respirable, aerosol clouds. Some of these observations (e.g. reducing both the concentration of non-volatile ingredients and the volume of the metering valve to produce more respirable aerosols) appear contradictory and unhelpful to the formulator who has a fixed drug dose to deliver. Fortunately however, the subject of suspension concentration is treated quite rigorously through Gonda's theories for aggregation (Gonda, 1985; Chan and Gonda, 1988) which enable calculation of the probable number of suspended particles which each propellant droplet can contain, provided that initial droplet sizes are presumed from a knowledge of the spray mechanics.

2.2. Effects of valve and actuator design

At this juncture in our discussion, we should emphasize that all of these observations followed studies of the 'emitted' aerosols and the ways in which their properties were modified by formulation. Given that the spray nozzles and the aerosol testing methods vary between investigators, it is difficult to attribute some of the other (historical)

work to the subject of formulation alone. Similarly, work on valves and actuators cannot be divorced from the effects of formulation. The work of Rance (1972, 1974)) on hairspray formulations showed the effects that different propellant blends and co-solvents could have on aerosol exit velocities, after these formulations had passed through different continuous valves with different orifice diameters and designs. Similarly, the aerosol 'droplet' size data of Pengilly and Keiner (1977) by necessity superimposes the valve and spray nozzle effects upon those due to the formulations. Essentially, we can observe from those studies that high pressure formulations exit small orifices faster; in some circumstances these formulations break into smaller droplet clouds but in others, they may deposit to greater degrees upon the actuator mouthpiece due to their higher impaction tendencies. Similarly, Bell et al. (1973) showed that low volatility solution formulations do not evaporate as fast as most suspension systems, resulting in lower respirable fractions of drug from the former, provided that aerosol size determination occurred before complete evaporation had occurred (patients inhale aerosol clouds prior to complete propellant evaporation). Conversely, using similar dynamic sizing techniques, Dalby and Byron (1988) showed that 0.1% solutions (compared to 0.1% drug suspensions) in 'identical volatile propellant systems, sprayed through identical actuators', provided smaller aerosols with greater respirable drug dose fractions. Different metering valve designs are also known to be more or less prone to cause variations in the drug dose from suspension systems (Cyr et al., 1991; Graham et al., 1992; Byron, 1994). The contents of metering valves held in contact with suspension formulations (valve-down storage; Fig. 1) may be enriched or depleted of suspended drug, dependent on the relative density of the drug and propellant (Byron, 1994). Smaller orifice diameters and/or longer nozzle paths in the actuator can also cause the production of smaller droplets, and/or deaggregation of suspended material, during the high speed passage and shear of the drug formulation through the nozzle. The data presented in Table 1 show clearly that increasing the pathlength (and shear) during the spray process for these experimental formulations caused a significant increase in deaggregation of suspended particles.

Table 1
Influence of spray nozzle dimensions on the deaggregation of suspended material[a]

Nozzle dimensions (mm)		Percentage agglomerates		
Length	Diameter	0.05% PS	0.1% PS	0.2% PS
1.05	0.49	2.0	3.3	5.5
0.65	0.50	2.6	4.0	6.2

[a] Propellant: 5% (w/w) ethanol in surfactant-free HFA 134a. Suspended material: 5 μm polystyrene spheres (PS) at 0.05, 0.1 and 0.2% (w/w). The percentage of agglomerates was defined and measured as (the number of spheres present in agglomerates/total number of spheres) × 100; following actuation through a primed 50 μl Bespak 357 inverted metering valve attached to spray nozzles with dimensions defined in the table.

Given this background information, and the knowledge that the MDI-system designer usually works to deliver a constant drug dose, the design, formulation, and manufacture of MDIs must be largely empirical and based upon the characteristics of the aerosol emitted for inhalation by the patient. Thus, the 'delivered dose' and the 'aerosol's aerodynamic particle size distribution' are most important, and provided these properties are reproducible, the appearance and behavior of what is inside the canister takes second place. Nevertheless, it is well recognized that delivered dose and aerodynamic particle size distribution are easily influenced by the methods used to determine them. Fortunately, over the last 10 years, the European and United States Pharmacopoeias have published standardized test procedures for determination of the delivered dose and aerodynamic size distributions from MDIs (United States Pharmacopoeia, 1998; European Pharmacopoeia Supplement, 1999a,b). These tests can and have been employed to enable the comparative assessment of CFC and HFA-reformulated inhalers (Leach, 1996) and are now gaining wider acceptance both in industry and academia. The use of such standard methods should enable the development of a much larger comparative database than before; this because standard methods

may make results from different laboratories comparable and therefore less mysterious.

2.3. Effects of method of preparation and storage

Variations in the size distribution of the milled micronized drug substance suspended in propellants, and the methods whereby this product is deaggregated, suspended and packaged, can all influence the aerosol output characteristics of MDIs (Lee and Hershey, 1977; Phillips and Byron, 1994; Ward and Schultz, 1995; Steckel et al., 1997). Clearly therefore, any attempt at selecting an optimal formulation must first ensure that each formulation being studied is appropriately prepared and controlled. Furthermore, it is quite possible to prepare fabulous aerosols on an individual basis that are impossible to make in a production run (Byron, 1990). As if this repeated demand for experimentation is not enough, formulators in industry are well aware of the difficulties in forecasting the effects of formulation and packaging on the long term stability of MDIs.

Delivered doses and aerodynamic size distributions from suspension systems may change as functions of dose number and storage orientation (valve-up or valve-down) over periods as short as a single dosing interval (Cyr et al., 1991; Byron, 1994; LeBelle et al., 1996; Cyr et al., 1997); problems that must be countered early in the development process, by modifying valve design during formulation and packaging studies. Over longer terms, high humidity, storage duration and/or increases in the water concentration inside containers (Miller, 1990), may cause aggregation of suspensions and erratic dosing. Propellant leakage in the absence of physical or chemical instabilities may cause dosage increases over time (McNamara, 1994, 1996). Crystal growth in suspension is thermodynamically inevitable over the long term (Phillips and Byron, 1994) and is clearly undesirable over, say a 2-year shelf-life; it may be seen as alterations in emitted aerodynamic size distribution. It may be accelerated by high temperature and humidity (Phillips et al., 1990), changes in water content (Miller, 1990), inappropriate choice of surfactant concentration (Phillips and Byron, 1994), temperature cycling, and the slow occurrence of propellant-drug substance interactions like solvate formation (Byron, 1990). Unpredictable interactions between drug substance and packaging components may involve sorption, nucleation (usually at a packaging-formulation interface) and thus, irreversible aggregation of suspended particulates promoted by surfactants (Murphy, 1997). All these effects may be accelerated or retarded by changing the formulation and/or packaging ingredients.

3. HFA formulations

3.1. Physico-chemical characteristics of HFA and HFA-ethanol blends

Improving the theoretical approach to the formulation of MDIs must begin with a proper understanding of the physico-chemical characteristics of the propellants and propellant-co-solvent blends which make up the bulk of each MDI's content. While there are a number of propellant alternatives to the CFCs (Fischer et al., 1989; Dalby, 1991; Dalby and Byron, 1991; Byron and Dalby, 1993a,b; Dalby and Byron, 1993), the pharmaceutical industry has focused most of its attention on HFA 134a and 227ea as the two toxicologically proven, non-ozone depleting, CFC alternatives for inhalation. HFA 134a has received most attention because it was available for testing in commercial quantities earlier than HFA 227ea. However, each of these HFAs, in the form of high vapor pressure liquified gases (their nature inside MDI canisters) differ in several major respects to CFC 12, the high vapor pressure propellant which forms the bulk of existing CFC formulations.

Fig. 2 shows the structure of these propellants; while CFCs are completely halogenated (and thus, have carbon skeletons shrouded entirely by large electronegative mantel atoms), the HFAs of interest to us have one (HFA 227ea) or two (HFA 134a) small, asymmetrically positioned, hydrogen atoms in their mantels. The enhanced electronegativity (fluorine is more electronegative than chlorine) in the halogen mantel of the HFAs creates a

Table 2
Physical properties of chlorofluorocarbon and hydrofluoroalkane propellants[a]

	BP	KB	δ	μ	ε	α
CFC 11	23.8	60	7.6	0.46	2.3	9.5
CFC 12	−29.8	18	6.1	0.51	2.1	7.9
CFC 114	3.6	12	6.4	0.50	2.3	8.5
HFA 134a	−25.8	8	6.6	2.06	9.5	5.4
HFA 227ea	−17.3	10	6.6	0.93	4.1	5.8

[a] BP: Boiling point (°C); KB: Kauri–Butanol value (Barton, 1983); δ: solubility parameter (cal/ml); μ: dipole moment (D); ε: dielectric constant (liquid); α: polarisability (10^{-24} cm^3/molecule, vapor). Adapted from Byron et al. (1994).

distinct dipole on the hydrogen-carbon bonds in both propellants. The high vapor pressures and low boiling points of these ethane and propane HFA derivatives (Tables 2 and 3), are thus misleading indicators of their non-polar natures. Even though the HFAs show relatively small intermolecular attraction (as liquids, the vast majority of their mantel atom interactions are repulsive, fluorine–fluorine electronegative collisions), we should expect to see evidence of increased polarity in each of these propellants when compared to the CFCs. Unfortunately, both the traditional Kauri-butanol value (KB) and the Hildebrand solubility parameter (δ), have been shown to be non-predictive of the differences in polarity and solvent properties of CFCs and HFAs (only the KB-value of CFC 11 differs substantially; Table 2). Conventional wisdom ascribes higher KB values to indicate increased solvency for solutes in propellants, while similar values, between propellants, for KB and the solubility parameter, δ, implies their similar solvent power. In practice, we will observe that the first three columns in Table 2 show that none of these physical parameters are good indicators of the solvency differences between CFCs and HFAs. The properties which reveal the greatest differences are shown in the last three columns of Table 2. Dipole moments (μ) and dielectric constants (ε) of each of the HFAs are reflective of the increased polarities of these propellants and are significantly larger than those of the CFCs. The polarizability (α) of the HFAs is smaller than that of the CFCs, reflecting the strength with which the fluorine atoms attract associated electrons ('refusing' to give them up), explaining the low boiling points and low intermolecular attraction in these propellants (increased values for (α) are

Table 3
Densities and vapor pressures of HFA 134a/227ea mixtures[a]

HFA conc. (%, w/w)		Density at 25°C (g/ml)		Vapor press. at 23°C (psia[b])	
134a	227ea	Theoretical	Actual[c]	Theoretical[d]	Actual[d]
100	0	1.205	1.205	98.9	98.9
90	10	1.221	1.220	97.2	96.0
80	20	1.238	1.235	95.5	95.5
70	30	1.254	1.252	93.5	94.0
60	40	1.271	1.268	90.9	94.3
50	50	1.289	1.286	88.9	93.1
40	60	1.307	1.304	86.3	90.6
30	70	1.326	1.323	83.4	85.7
20	80	1.344	1.342	80.2	82.3
10	90	1.361	1.363	76.5	76.4
0	100	1.385	1.385	72.2	72.2

[a] Theoretical density and vapor pressure were calculated using Eqs. (1) and (2), respectively (see text).
[b] One atm = 14.7 psia = 101.3 kPa.
[c] Means of replicate ($n = 3$) determinations using a Paar densitometer modified to retain liquified gases at their respective vapor pressures.
[d] Means of replicate ($n = 3$) determinations using a propellant-purged pressure gauge. Unites are pounds per square inch absolute (psia).

Table 4
Water solubility in chlorofluorocarbon and hydrofluoroalkane propellants

Propellant	Water solubility at 25°C (ppm)	
	Pure propellant[a]	Prop. + 10% (w/w) EtOH[b]
CFC 11/12	100	na[c]
CFC 12/114	91	na
CFC 12	Na	9900
HFA 227ea	610	11000
HFA 134a	2220	13500

[a] Adapted from Williams (1998).
[b] Adapted from Gelotte and Shadeed (1998).
[c] Not obtainable.

directly proportional to increased intermolecular attractive 'London' forces).

These physical properties of HFA 134a and 227ea are responsible for many of the product re-formulator's experimental observations, 'problems' and solutions to these 'problems'. As more data has become available, the solvency differences and differences in polarity of the HFAs have become clear. Table 4 shows water solubility data from the literature and indicates a striking difference between the CFCs and the HFAs, the latter having a much greater 'attraction' and liking for this small, high polarity solute. Gelotte and Shadeed's latest data (Gelotte and Shadeed, 1998) show that this property is carried through into HFA-ethanol blends, implying that dipolar interactions between HFAs and ethanol itself (at 10% by weight and 1/4.1 or 1/2.4 by mole ratio, ethanol:HFA134a and ethanol:HFA227ea, respectively) were not capable of completely displacing HFA-water attractions in this liquid milieu. The solubility of water in HFA 134a is significantly greater than that in HFA 227ea on both weight (Table 4) and mole fraction scales (mole fractions of water in pure HFA 134a and 227ea are 0.012 and 0.006, respectively), reflecting no doubt, HFA 134a's larger number of available hydrogen-carbon dipole's (Fig. 2). This enhanced water solubility (HFA 134a > HFA 227ea > CFC 12) has also been shown for drug solutes (Byron et al., 1994), showing the probable importance of the hydrofluoroalkane propellants' electropositive proton(s), as sites for solute-solvent dipole-dipole attractive interactions. This property enables the possibility of pressurized drug solution formulations in some cases, however, higher ingress rates of water into HFA-MDIs, may decrease shelf-lives due to enhanced physical and chemical degradation rates resulting from enhanced water uptake, following storage in humid environments (Miller, 1990; Williams, 1998).

Thus, the solvent properties of these alternative propellants must be carefully examined; this difference between CFCs and HFAs being one of the major reasons that extensive reformulation work is required. With the benefit of the explanation furnished above, it should not be surprising that the low HLB, hydrophobic surfactants (sorbitan trioleate (Span 85), oleic acid and lecithins), used for years in CFC formulations, are effectively insoluble in HFAs (Byron et al., 1994). These 'inhalation-approved' surfactants can only be used effectively in propellant blends containing co-solvents like anhydrous ethanol which enable their dissolution (Purewal and Greenleaf, 1990). If surfactant(s) is required in a co-solvent-free formulation, for purposes like dispersion, solubilization and/or valve lubrication, then surfactant dissolution can only be accomplished by the choice of alternative surfactants. In line with our earlier observations concerning the polarity of the HFAs, more hydrophilic surfactants (with higher HLB-values) tend to dissolve much more readily (Table 5). However, because surfactant solubility (and for that matter drug solubility) in pure HFAs is heavily reliant upon the ability to form dipole–dipole interactions between the solute and the liquid propellant, it is not surprising that the addition of small amounts of competing dipolar molecules (like water) can cause rapid, irreversible precipitation (phase separation; Blondino and Byron, 1998). Thus, strict control of impurities like water are essential in the production and storage of co-solvent-free HFA-drug formulations.

The properties of HFA 134a–HFA 227ea mixtures, and propellant-co-solvent blends, offer some further useful insights into the nature of these liquified gases, when these are maintained in equilibrium with their own vapors in individual MDIs (Fig. 1). Work performed in our laborato-

ries several years ago (unpublished data) focused on the density and vapor pressure of HFA 134a, HFA 227ea and their admixtures in the presence and absence of anhydrous ethanol. All three of these materials are freely miscible in all proportions and offer the formulator the possibility of manipulating vapor pressure and density to achieve an appropriate end product. When density was studied at 25°C, using a high precision modified Paar densitometer (Anton Paar S.A., Graz, Austria), there were no deviations from theory, and thus no contraction or expansion following mixing. Over the concentration ranges investigated HFA 227ea and HFA 134a formed ideal mixtures, with and without anhydrous ethanol. Values for density which were determined experimentally (Table 3 and Fig. 3(A)), could not be distinguished from theoretical predictions based on Eq. (1):

$$1/d_{\text{mixture}} = ((g_a/g_{\text{mixture}})/d_a) + ((g_b/g_{\text{mixture}})/d_b) \quad (1)$$

where, d and g represent density and mass, respectively, and subscripts a and b represent the components of the mixture (HFA 134a, 227ea or ethanol). These observations implied that intermolecular forces between ethanol (up to 30% by weight) and each of the HFAs, as well as between HFA 134a and HFA 227ea (in all proportions) had similar orders of magnitude. Following admixture with ethanol we were able to predict density values without recourse to exhaustive experimentation. This was not seen with vapor pressure predictions. In these cases, when ethanol was added to either of these HFAs, and gauge pressures were determined following packaging with continuous valves, there were large positive deviations from Raoult's law; HFA–ethanol admixtures having higher equilibrium vapor pressures than predicted from Eq. (2) below (Fig. 3(B)):

$$\text{vp}_{\text{mix}} = (\text{vp}_{134a} \times \text{mf}_{134a}) + (\text{vp}_{227ea} \times \text{mf}_{227ea}) \quad (2)$$

where vp and mf represent vapor pressure and mole fraction, and subscripts 134a and 227ea

Table 5
Apparent solubilities of surfactants in propellants[a]

Surfactant	HLB[b]	Apparent solubility[c] (%; w/w) in[d]:		
		CFC 11	HFA 134a	HFA 227
Oleic acid	1.0	∞	<0.02	<0.02
Sorbitan trioleate	1.8	∞	<0.02	<0.01
Propoxylated PEG[e]	4.0	∞	≈3.6	1.5–15.3[f] 32.0–60.3[f]
Sorbitan monooleate	4.3	∞	<0.01	<0.01
Lecithin	7.0	≈22.7	<0.01	<0.01
Brij 30	9.7	∞	≈1.8	0.8–1.2
Tween 80	15.0	≈0.1	<0.03	0–10.0[f] 25.0–89.8[f]
Tween 20	16.7	≈0.1	≈ 0.1	1.4–3.5
PEG[e] 300	20	<0.01	≈4.0	1.5–4.3[f] 16.1–100[f]
PVP, PVA[g]			>0.1	
Oligolactic acids			≈2.7[h]	

[a] Adapted from Blondino and Byron (1998), except when noted.
[b] Hydrophyloc-lipophilic balance.
[c] Determined as the maximum % (w/w) to produce a single clear phase.
[d] ∞: Appeared soluble in all proportions; ≈: approximately equal to.
[e] Polyethylene glycol.
[f] Existed as one clear phase only in this concentration range.
[g] Polyvinylpyrrolidone, polyvinylalcohol.
[h] Duan et al. (1998).

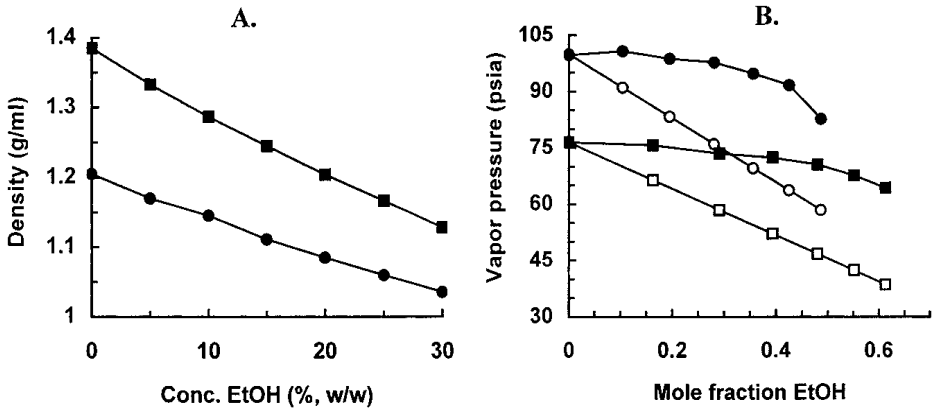

Fig. 3. Densities and vapor pressures of HFA 134a and 227ea as functions of added ethanol concentration. (A) Experimentally determined values for density (25°C): (●) HFA 134a, (■) HFA 227ea; the theoretical curve, assuming ideal mixing (see text), could not be distinguished from experimental data. (B) Vapor pressure (21.5°C): HFA 134a: (○) theoretical, (●) actual; HFA 227ea: (□) theoretical, (■) actual. Theoretical density and vapor pressure were calculated using Eqs. (1) and (2), respectively (see text).

represent HFA 134a and 227ea, respectively. The combined observations (recently also described by Tzou, 1998) in Fig. 3 appear to defy conventional wisdom; deviations from Raoult's Law are frequently accompanied by density changes. Typical examples are the case of ethanol–water (negative deviation from Raoult's law, contraction on mixing) and acetone–carbon disulfide (positive deviation from Raoult's law, expansion on mixing). Possibly, the behavior shown in Fig. 3 is an indication that each of the HFA propellants had a higher affinity for the gas–liquid interface than the ethanol, the latter being preferentially enclosed by an HFA molecular matrix. Whatever the explanation, this behavior enables substantial addition of co-solvent ethanol (and enhanced solvent power in the blend), without detrimental reductions in vapor pressure and aerosol performance (Moren, 1978b; Newman et al., 1982; Dalby and Byron, 1988). The data show how little is understood about the behavior of these pressurized systems on a molecular level and indicate that the surface concentrations of dissolved ingredients, as seemingly innocuous as ethanol, may not be entirely predictable from a knowledge of their concentration in the bulk liquid.

Based on the vapor pressure data presented in Fig. 3 and Table 3, HFA propellants, both in the presence and absence of ethanol, may allow the formulator to increase the efficiency of existing (CFC) MDIs, with respect to their production of respirable aerosol. Alternately, our observations pose a problem to formulators who wish their products to show equivalent drug delivery efficiencies to CFC products. Most of the HFA propellant blends have much larger vapor pressures than some frequently used CFC mixtures (Table 6) and are thus able to produce smaller more respirable aerosols (Polli et al., 1969; Moren, 1978b; Newman et al., 1982). Because there is no 'low pressure' HFA alternative to CFC 11 (Table 2), only ethanol or presently untested additives can be used to reduce operational vapor pressures in new MDIs. This has meant that some product development teams, seeking to establish similar performance profiles for their HFA-reformulated products, have studied and developed alternative actuators with different spray characteristics. Such systems require extensive clinical testing to revalidate product performance in pa-

Table 6
Vapor pressure of some frequently used CFC-blends in suspension MDIs[a]

Concentration (%, w/w) CFC 11/12/114	Vapor pressure at 21°C (psia[b])
25/50/25	56.8
28/72/0	66.9
0/60/40	67.6

[a] Adapted from Byron, 1990.
[b] One atm = 14.7 psia = 101.3 kPa.

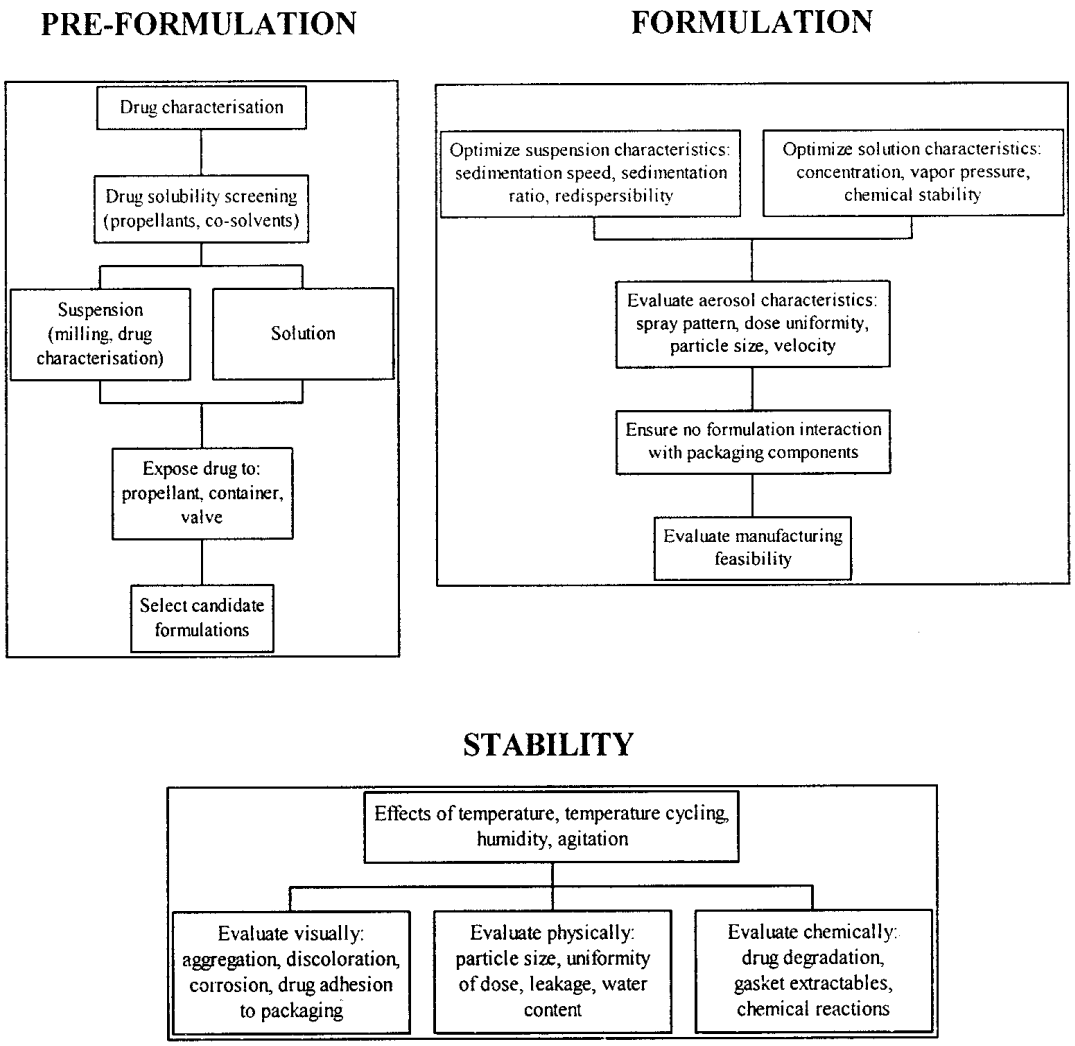

Fig. 4. Flow chart showing some of the necessary steps in pre-formulation, formulation and stability assessment of MDIs.

tients (Leach, 1996). Because the density of most drugs is similar to the density of the new HFAs, density differences between suspended drug and propellant blend may be minimized by the formulator (Table 3 and Fig. 3) with commensurate improvements in dosing uniformity (Byron, 1994). Temperature-dependencies of both density and vapor pressure remain, of course, as complicating factors for the product formulator. Both of these are relatively unaffected by the change from CFC to HFA propellants.

3.2. Drug substance

Fig. 4 shows a flow chart covering MDI development, and involving pre-formulation, formulation and stability assessment. While this rather general scheme is not valid for all formulation studies, the early focus on drug solubility in propellants and different propellant–co-solvent blends allows the formulator to decide whether a suspension or a solution MDI is most appropriate. Measurable solubility in the propellant is usually an indication of crystal growth problems which are likely to be seen during storage of the micronized drug substance in suspension formulations. Determination of drug solubility in pure propellant and propellant blends, in the presence and absence of surfactants and co-solvents, can be accomplished using the filtration apparatus and method of Dalby et al. (1991); early indications of crystal growth can be seen most readily using

microscopy (Phillips et al., 1993). As a general rule, suspension MDIs should ideally be formulated with drug substances which are insoluble in the continuous phase. However, if dose requirements are such that a suspension of partly soluble micronized drug substance must be utilized, then a blend should be selected which minimizes dissolution and dependence of drug solubility on temperature. In this way, crystal growth due to temperature cycling should occur most slowly. This phenomenon, known as Ostwald ripening (Mullin, 1972), is due to entropy favoring the dissolution of smaller micronized particles and drug re-crystallization on larger particles. This can result in less reproducible dosing and/or increases in the aerodynamic size distribution of each delivered dose (Phillips et al., 1990); both effects can limit the shelf life of the final product during stability testing (Fig. 4).

In the event that studies show that crystal growth in propellants may become a problem, the formulator has several options. For suspension formulations these may involve changing the physical form of the drug substance itself (salt selection), minimizing amorphous content and selecting the most stable polymorph, and modifying drug substance surface characteristics to retard the rates at which dissolution and reprecipitation can occur. Presumed, in this part of our discussion, is the need to avoid the use of cosolvents which increase solubility. Probably therefore, such suspension formulations will be prepared in pure propellant(s) with added suspending agent(s). This fact alone complicates the MDI manufacturing process by requiring either cold-filling of the whole formulation, followed by valve addition and crimping, or pressure filling a suspension, through the crimped valve, into pre-evacuated or purged canisters. Selection of an alternate drug salt which is insoluble in the selected blend is probably the most effective option. When this is possible (e.g. HFA-albuterol, from 3M Pharmaceuticals, contains suspended albuterol sulfate and ethanol, while the CFC formulation contains the suspended base) the solubility of true salts in these aprotic solvents is predictably much lower than that of free bases or acids (Tzou et al., 1997). With non-ionic drug substances like the anti-inflammatory steroids however, this simple chemical maneuver is precluded, and the formulator is left to minimize the amorphous content of the micronized drug product and/or to search for less soluble (more stable) polymorphic forms. One further way of manipulating the rate of crystal growth in a problem formulation relates to the choice and concentration of surfactant selected as suspending agent. The effects of these variables, which are highly drug substance dependent, can only be determined by experiments in which the kinetics of particle size growth are compared between formulation options. Isothermal methods have been reported by Phillips et al. (1990), and acceleration of Ostwald ripening can be accomplished most readily by temperature cycling. Importantly, Phillips and Byron (1994) have noted that the choice of surfactant, and its concentration, can be critical.

It is always important to be aware that the drug substance comminution technique determines many of the final product's characteristics (Lee and Hershey, 1977; Ward and Schultz, 1995; Steckel et al., 1997). Phillips and Byron (1994) reported on the higher amorphous content of methylprednisolone after micronization, and its crystal growth consequences in model MDI formulations. Virtually all milling techniques cause partial disruption of crystalline materials and it is essential that characterization of the drug substance (microscopic examination, calorimetry, thermal gravimetry and chemical assay) be performed both before and after particle size reduction (Fig. 4). Although air jet milling, ball milling or microcrystallization are the most frequently used size reduction techniques, conventional spray drying (Naini et al., 1996; Dasovich et al., 1998) and supercritical fluid spray drying (Gallagher-Wetmore et al., 1994; York and Hanna, 1996; Steckel et al., 1997) are also possibilities. While spray drying usually produces an amorphous product with a high solubility, recent work on spray drying from supercritical fluids has shown that it is possible to produce 'micronized' high crystallinity drug particles with clean, predictable surface characteristics. This process also shows great promise as a means of reducing the present production variability which is usually associated

with batches of micronized drug product (York et al., 1998).

The combined knowledge of the drug dose and its dissolution behavior in propellant-co-solvent blends may indicate that a solution formulation could be prepared. In this case, non-ionic forms of the drug substance will be preferred and it may be possible to increase the respirable fraction above that seen with a CFC-based suspension product (Dalby and Byron, 1988; Leach, 1996). The use of HFAs can be an advantage over CFCs in this respect, due to their greater polarity and solvency for many non-ionic drugs (Byron et al., 1994). One possible drug candidate for a solution MDI formulation is beclomethasone dipropionate (BDP). Table 7 lists its solubility in CFC 12, HFA 134a and 227ea and the corresponding dose of BDP delivered per 50 μl metering volume. Because the US label claim of BDP is 42 μg per spray, and BDP is freely soluble in ethanol, it is clear that the addition of a limited amount of ethanol to HFA 134a allows the formulation of a solution MDI. It is possible also, that surfactants and other partially polar materials may be employed to enhance the solubility of drugs in HFAs. The formulator's major concerns with solution systems are reduced chemical stability (Soine et al., 1992) and drug loss by partitioning into gasket materials. The latter may be overcome by valve selection and/or by including drug overage in the formulation. Chemical stability problems however can be enhanced or retarded by choice and concentration of surfactants in some cases (Fig. 5, Blondino and Byron, 1996) and are

Table 7
Estimated solubilities of beclomethasone dipropionate (BDP) in CFC 12, HFA 134a, HFA 227ea and 10% (w/w) EtOH in HFA 134a (21°C), expressed as μg/mg and μg/50 μl (a typical metering volume) propellant

Propellant	Solubility	
	μg/mg	μg/50 μl
CFC 12	0.003	0.2
HFA 227ea	0.1	7
HFA 134a	0.3	18
HFA 134a + 10% EtOH	>0.88	>50

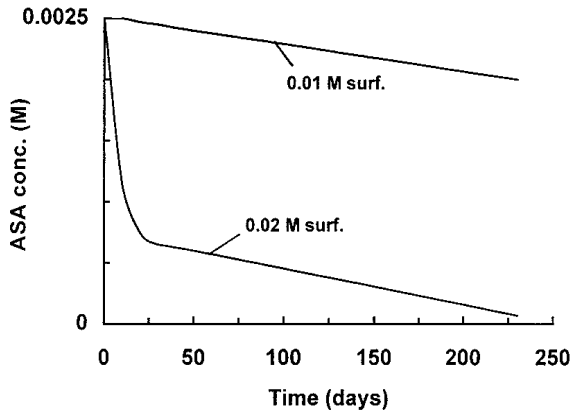

Fig. 5. Degradation of acetyl salicylic acid (ASA) in solution in CFC 11, as a function of time and surfactant concentration. Surfactant: sorbitan trioleate (Span 85) at concentrations of 0.01 and 0.02 M. Adapted from Blondino (1995).

unpredictable phenomena whose effects should be screened and minimized during development (Fig. 4).

Finally, in this section, pre-formulation studies may indicate interactions between the drug and other unavoidable formulation components (Fig. 4). A good example of this is found in the solvate formation seen between beclomethasone dipropionate (BDP) and propellants. Micronized BDP exposed to CFC11, quickly forms a solvate whose thermogram is illustrated in Fig. 6. The magnitude of the exothermic transition seen at about 120°C can be variable and is due to the non-stoichiometric association of the drug substance with propellant (BDP melts at about 212°C). This solvate formation with CFC11 demands that the CFC suspension formulation be prepared with the micronized, preformed solvate, which is then marketed as an MDI containing the 'steroid-clathrate with CFC11'. Interestingly, the solvate retains its solvent until quite high temperatures are reached (Fig. 6). In our laboratories, we have compared the formation and characteristics of BDP-CFC11 solvates with those of other propellants (Dalby and Byron, 1993). The results of those studies indicated that it was fortunate that a solution formulation was possible with BDP; this because BDP forms a solvate with HFA 134a much more slowly over a time scale of months, when the two materials are mixed in suspension formulations. This solvate formation with HFA 134a resulted in

a slow but progressive crystal growth of initially micronized BDP in suspension.

3.3. Surfactant behavior

Hydrophobic surfactants like sorbitan trioleate and oleic acid, dissolved in the pressurized liquid phase of CFC-based MDI formulations, have served, at least in part, to lubricate the valve and its components during the depression and release cycle associated with container emptying. As the industry has moved toward a wide variety of different HFA formulations, some of which possessed little or no lubricity, valve manufacturers have sought to improve the performance of their components. As a result of these developments, it is now possible to purchase valves which function repeatedly even in the absence of oily surfactants. As a result, formulations are now reaching the market which challenge the conventional wisdom that surfactants are a necessary component of MDIs. Clearly, stable solution formulations, with or without co-solvents, should be able to function without surfactants, provided valve elastomers and valve designs exist which are capable of storage and repeated firing, in the presence of liquid and headspace exposure to these new formulations. Clearly, much of the valve and elastomer design and construction work in this area is proprietary; but multiple elastomers in each and every metering valve must possess correct dimensional curing properties (when exposed to the formulation), neither sorb drug excessively, nor leach toxic extractables, retain the higher vapor pressure formulation with minimal leakage (Table 3 and Fig. 3) and exclude environmental water as it seeks to permeate container seals.

While surfactants in HFA solutions may still be used to increase drug solubility, alter the temperature dependence of solubility (to prevent precipitation) and overcome intractable valve sticking problems, in suspension MDIs they have additional functions. These include prevention of irreversible caking, minimizing drug particle adhesion to container walls and valve components and retarding overly rapid separation between the

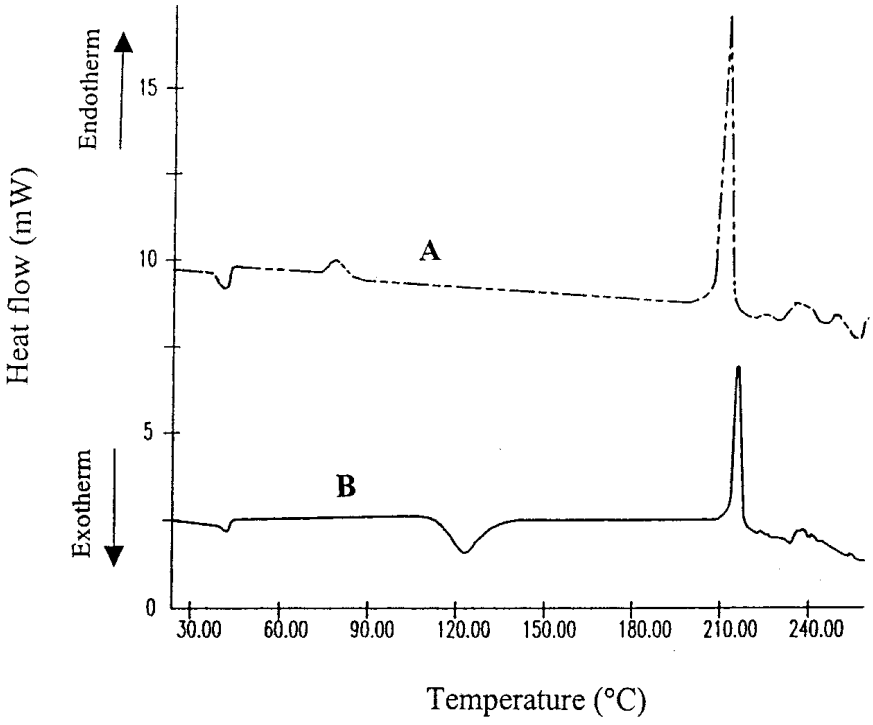

Fig. 6. Differential scanning calorimetry (DSC) thermograms of (A) beclomethasone dipropionate and (B) beclomethasone dipropionate—CFC 11 solvate. The exotherm at 110–135°C, in the case of the solvate, is due to solid phase desolvation. The onset of the drug's melting endotherm commences at 212°C.

solid and liquid phase. The theoretical approach to the stability of suspensions usually invokes the DLVO-theory (Hiestand, 1964; Parkins, 1986), which states that a stable, redispersable suspension can be formed via controlled aggregation or 'flocculation' (Ranucci et al., 1990). The conventional wisdom behind this approach states first that 'deflocculated' suspended systems are unstable, and that they will flocculate irreversible over time. After complete sedimentation (or 'creaming' if drug is less dense than continuous phase) has occured, the van der Waal's forces between drug particles will be large enough to cause irreversible caking; this because particles are too close, so that the interparticulate potential energy is negative and described by the magnitude of the system-dependent 'primary minimum' (Martin, 1993). 'Controlled flocculation' searches to establish a 'secondary minimum potential energy' at an interparticulate distance where the van der Waal's forces between particles are lower; such a system (which still separates over time) should have a larger sedimentation volume (Hickey et al., 1988; Ranucci et al., 1990) and be much easier to redisperse.

The problem with this otherwise plausible theory concerns its foundation in aqueous media, where much 'suspension stabilization' is brought about by modifications in the ionic electric double layer which surrounds individual particles (Schneider et al., 1978). These electrostatic theories (Hiestand, 1964; Martin, 1993) have never really been challenged or validated with respect to the stabilization of non-aqueous drug suspensions in MDIs. Particulate charge, which may be present as a result of triboelectrification, may not be distributed uniformly on particle surfaces and may even be bipolar in nature (Wyatt and Vincent, 1992; Byron et al., 1997; Peart et al., 1998). Even if electrostatic charges are uniform across particles, electronic repulsive forces should be much smaller in these low dielectric propellant media (Fig. 7). Note especially, that ion concentrations in propellants must, by definition, be very low; thus, repulsive forces between particles are probably much lower than those indicated in Fig. 7. In the absence of surface electrostatic charges on particles, and assuming interparticulate distances which exceed electronic van der Waal's radii, the only remaining repulsive force between particles is conferred sterically following the adsorption of surfactant to each particle's surface. Thus, manipulating the steric forces (hindrance between surfactant molecules' tails which extend from the surface into the medium) is the theoretical key to stabilizing a suspension MDI. These forces are manipulated by varying the type and concentration of surfactant, thus allowing the formulator to optimize suspension characteristics such as sedimentation speed, sedimentation ratio and redispersibility (Ranucci et al., 1987). Unfortunately, only experiment enables the formulator to determine whether a particular surfactant is capable of stabilizing a given drug substance and, even following such work, the observations can be misleading. Suspensions with apparently ideal physical characteristics do not necessarily yield the best aerosols (Hickey et al., 1988) and ease of redispersion does not guarantee the breakdown of agglomerates into primary particles (shear forces during actuation and spraying may also contribute to deaggregation).

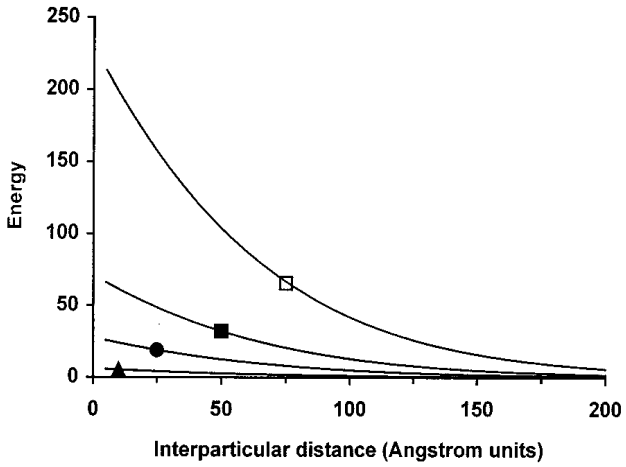

Fig. 7. Electronic energy of repulsion (calculated according to Schneider et al., 1978) between 1 μm solid particles as functions of the dielectric constant of the medium and interparticular distance. Positive energies indicate repulsive forces. Equal zeta-potentials (25 mV) were assumed in all media. The Debye–Huckel term (reciprocal thickness of the diffuse double layer) was set at $2 \cdot 10^6$ cm^{-1}. (▲) CFC 12, dielectric constant (ε): 2.13; (●) HFA 134a, ε: 9.51; (■) ethanol, ε: 24.3; (□) water, ε: 78.36. 1 Angstrom unit = 10^{-8} cm.

In the absence of co-solvents like ethanol, the use of HFAs forces formulators to use different surfactants. The low HLB materials used in CFC propellants (sorbitan trioleate (Span 85), oleic acid and lecithin) are insoluble in HFAs (Purewal and Greenleaf, 1990; Byron et al., 1994). More hydrophilic surfactants, with higher HLB-values, tend to dissolve more (Table 5) in HFAs. As surfactant solubility (and for that matter drug solubility) is highly dependent on the composition of the medium (Blondino and Byron, 1998), it is essential to control the water content during manufacture and storage. While it is generally assumed that surfactants need to dissolve in propellant to be effective, some reports in the literature indicate that even insoluble surfactants may be effective suspension stabilizers when their surface associations are strictly controlled. Byron et al. (1994) showed that precoating albuterol with oleic acid—prior to suspending the coated particles in HFA 134a—was efficient in retarding the drug's creaming from suspension over a period of 30 s, the creaming speed was highly dependent on the surfactant/drug ratio. In the patent literature Johnson (1992) claimed a suspension stabilizing effect for perfluoroalkanoic acids, potassium perfluoroalkyl sulfonates and ammonium perfluoroalkyl carboxylates, mentioning that these surfactants were 'soluble' in HFA 134a. However, Byron et al. (1994) noted that the solubility of perfluorooctanoic acid (which Johnson's patent claimed to be one 'surfactant of choice') was certainly less than 0.1% by weight. These examples demonstrate that surfactant solubility in propellant may not need to be high, in order to stabilize a suspension. Nevertheless, 'sufficient' solubility is a prerequisite if the product formulator wishes to have a margin of safety in which to operate; observe, for example, the need to prevent phase separation in a product, when manufacture and storage occurs at a variety of different temperatures and humidities (Blondino and Byron, 1998).

Surfactants, of course, may also be used to enhance drug solubility in certain media. Unlike the well documented presence of reverse micelles in hydrocarbons (Evans et al., 1988, 1989, 1990, 1991) and CFCs (Matthews and Hirschhorn, 1953; Fendler, 1982; Luisi et al., 1988; Eastoe et al., 1990; Walde et al., 1990), Blondino (1995) used light scattering and found no indication of reverse micellization in HFA 134a despite screening numerous surfactants. Dissolved surfactant molecules with high HLB values were present as monomers or very small molecular agglomerates.

The affinities of different surfactant molecules for the various interfaces in HFA-MDI formulations (e.g. gas–liquid, drug–liquid, container–liquid, etc.) can only be deduced following careful experimentation. During recent work in our laboratory in which we attempted the optimized formulation of polystyrene spheres in MDI suspensions, we found that we were unable to make predictions about the behavior of a large number of surfactants in 5% ethanol–HFA 134a blends. In general, drug and polystyrene spheres suspended in HFAs tend to show increased affinities for container surfaces. We have found little evidence to dispel our current belief that that this phenomenon is due more to repulsion by the propellants than attraction by alternate surfaces in the container; this is possibly because of the predominant electronegative mantel of the HFAs. As a result, suspended solids often appear to prefer to settle on HFA-depleted surfaces; then, if they possess any solubility in the propellant blend, crystal bridges form which preclude redispersion in the formulation. Provided however, interparticulate adhesion of this nature can be prevented, as is the case with polystyrene spheres, redispersion can usually be accomplished quite readily.

4. Conclusions

This review has attempted to describe the current state-of-the-art surrounding the formulation and reformulation of pressurized inhalers containing hydrofluoroalkane propellants. Relevant theory has been described wherever it exists. However, frequent gaps in our knowledge and theory have been identified, where an empirical approach to formulation continues to be essential.

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